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09/978,498	10/15/2001	Adrian Clausell	2055-181	4848

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EXAMINER	
PRATS, FRANCISCO CHANDLER	
ART UNIT	**PAPER NUMBER**
1651	9

DATE MAILED: 07/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/978,498	Applicant(s) CLAUSELL ET AL.	
	Examiner Francisco C Prats	Art Unit 1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5-55* is/are pending in the application.

4a) Of the above claim(s) *23-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5-22 and 38-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The amendment filed May 21 2003, has been received and entered. The text of those sections of Title 35, U.S. Code, not included in this action can be found in a prior office action.

Claims 1-4 and 56-95 have been cancelled.

Claims 5-55 are pending.

Election/Restrictions

Applicant's election of the group II invention, claims 5-55, in Paper No. 8 filed May 21, 2003, is acknowledged. Applicant's election of the species wherein the enzyme assayed is caspase, the uptake-enhancing agent is glycerol, and the indicator moiety is rhodamine 110 is also acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 23-37 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected species of invention, there being no allowable generic or linking claim. As discussed immediately above, election was made **without** traverse in Paper No. 8 filed May 21, 2003.

Note that claims 5-19 and 38-55 read on the elected species of invention. However, claims 20-22 (using DMSO as an uptake-

enhancing agent) have been examined in view of the art cited herein, and in the interest of compact prosecution.

Claims 5-22 and 38-55 are examined on the merits to the extent they read on the elected species (caspase, glycerol, rhodamine 110), as well as the use of DMSO as an uptake-enhancing agent for intact cell enzyme assays.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 9, 10, 54 and 55 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 9 is confusing, and therefore indefinite, because it requires the substrate/analyte to be mixed with the uptake-enhancing agent. The confusion lies in the fact that claim 9 depends from claim 1, which states that the incubation of substrate/analyte takes place "in the presence of an agent that enhances uptake of said substrate or analyte [.]" Thus, it is

confusing what is encompassed by claim 9, since claim 1 already requires the substrate/analyte and uptake-enhancing agent to be mixed. Because claim 54 contains the same limitation as claim 9, and ultimately depends from claim 1, claim 54 is indefinite for the same reasons as claim 9.

Claim 10 is confusing, and therefore indefinite, because claim 10 requires the substrate or analyte to not be mixed with the uptake-enhancing agent during incubation. The confusion lies in the fact that claim 10 depends from claim 1, and claim 1 states that the incubation of substrate/analyte takes place "in the presence of an agent that enhances uptake of said substrate or analyte [.]" Thus, claim 10 cannot logically depend from claim 1 because claim 10 excludes a limitation explicitly required by claim 1. Moreover, it is unclear how the claimed process can possibly be performed without mixing the ingredients required for the assay. That is, as claimed, claim 10 appears to be a physical impossibility. Claim 55, which ultimately depends from claim 1, also excludes the mixing of the various ingredients, despite claim 1's requirement of incubation together. A holding of indefiniteness over the cited claims is clearly required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 5-9, 13 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Los et al (Nature 375:81-83 (1995)).

Los et al disclose a process whereby ICE activity, i.e. caspase activity (see applicant's specification at page 4, lines 28-29), is assayed in intact CHO L929-APO-1 cells and SKW 6.4 cells, by measuring the rate of cleavage of a fluorogenic substrate over time. See Fig. 1, and accompanying legend. Los used 0.05% digitonin to permeabilize the cells to enable entry of the fluorogenic substrate. See id. A holding of anticipation over the cited claims is clearly required.

Claims 5, 9, and 15-19 are rejected under 35 U.S.C. 102(b) as being anticipated by Wansink et al (J. Cell Biol. 122(2):283-293 (1993)).

Wansink et al disclose a process whereby incorporation of BrUTP into RNA is measured over time in permeabilized human bladder carcinoma cells. See Fig. 1, page 285. The cells were permeabilized using a buffer comprising 25% glycerol, the elected species of uptake-enhancing agent. See page 284, left hand column, section entitled "*BrUTP Incorporation in Permeabilized Cells (Run-on Transcription)*", subsection entitled "*Cells in Suspension.*" A holding of anticipation of the cited claims is clearly required.

Claims 5, 9, 13-15, 20, 21, 46 and 54 are rejected under 35 U.S.C. 102(b) as being anticipated by Lucas et al (U.S. Pat. 5,698,411).

Lucas discloses the use of derivates of elected species of indicator moiety, rhodamine 110, in assays of whole cell enzyme activity. See abstract. Lucas discloses that additional agents, such as DMSO, preferably at 5%, may be used to assist the transfer of the assay compounds into cells. See column 29, line 61 through column 30, line 40. Lucas therefore clearly

describes the subject matter in the cited claims. A holding of anticipation is therefore required.

Claims 5-9, 13-15, 38-40, 46, 48-51 and 54 are rejected under 35 U.S.C. 102(a) or 35 U.S.C. 102(e) as being anticipated by Zhang et al (U.S. Pat. 6,248,904 B1).

Zhang discloses the use of derivates of the elected species of indicator moiety, rhodamine 110, in assays of whole cell enzyme activity, including caspase activity, for the purpose of ascertaining apoptotic as well as anticancer efficacy of therapeutic agents. See abstract. Zhang discloses that additional solubilizing agents, such as DMSO, as well as liposomes or detergents, may be used to assist the transfer of the assay compounds into cells. See column 39, lines 48-64. Zhang therefore clearly describes the subject matter in the cited claims. A holding of anticipation is therefore required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at

> the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 5, 11, 12 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lucas et al (U.S. Pat. 5,698,411).

As discussed above, Lucas discloses the use of the derivates of elected species of indicator moiety, rhodamine 110, in assays of whole cell enzyme activity. As also discussed above, Lucas discloses that additional agents, such as DMSO, preferably at 5%, may be used to assist the transfer of the assay compounds into cells. Lucas differs from the claimed subject matter in failing to explicitly disclose a single embodiment combining the uptake-enhancing agent with multiple enzyme assays, either simultaneous or sequential, as recited in claims 11 and 12, or the use of 20 to 60% DMSO as the solubilizing agent, as recited in claim 22.

However, Lucas clearly discloses that adequate analysis of the disease states of cells requires multiple enzyme assays,

with the generation of a specific data matrix for a number of different enzymes. See discussion at columns 43-48. The artisan of ordinary, recognizing that the enzyme assays would have been suitably performed either sequentially or simultaneously, clearly would have been motivated to have performed the assays using either tactic, reasonably expecting to generate the required data set. Thus, the claimed combination of uptake-enhancing agent with multiple enzyme assays clearly would have been obvious in view of Lucas' disclosure, the artisan of ordinary skill recognizing the advantages of solubility agents as disclosed by Lucas, and also recognizing the suitability of multiple enzyme assays to generate the data set disclosed by Lucas as being required for accurate disease diagnosis. A holding of obviousness over claims 11 and 12 is therefore required.

As to the amount of DMSO recited in claim 22, note specifically that Lucas clearly discloses that suitable amounts of solubilizing agent can be determined by optimization. See column 30, lines 13 and 14 ("The effective amount of solubilizing component may be empirically determined . . . ."). Because Lucas considers the concentration of solubilizing component to be a result-effective parameter which can be routinely optimized, the claimed concentration of DMSO must be

considered obvious absent some demonstration that said concentration confers an unexpected result upon the claimed subject matter. A holding of obviousness is therefore required over claim 22.

Claims 5, 13 and 38-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Landrum et al (U.S. Pat. 5,976,822) in view of Lucas et al (U.S. Pat. 5,698,411).

Landrum discloses the use of derivates of the elected species of indicator moiety, rhodamine 110, in assays of whole cell enzyme activity, including caspase activity, for the purpose of ascertaining apoptotic cells, as well as for the purpose of distinguishing apoptotic cells from necrotic cells. See Example 10, at column 22, line 34 through column. See also, abstract. Note specifically the use of different substrate moieties for different enzymes, disclosed at Table 1, column 22, lines 1-19. Landrum differs from the claims in that Landrum does not disclose the use of uptake-enhancing agents in the assays.

However, Landrum clearly discloses that additional ingredients, including "solubilizing components" can be used to improve the assays conducted according to the disclosure therein. See column 10, lines 21-37. Moreover, Lucas clearly

discloses that intact cell enzyme assays using rhodamine 110 derivatives can benefit from the addition of solubilizing agents which allow the assay compound to pass into the cell. See column 29, line 61 through column 30, line 40. Thus, the artisan of ordinary skill at the time of applicant's invention clearly would have recognized from Lucas the advantages of solubilizing agents in assays using rhodamine 110 derivatives as assay compounds. The artisan of ordinary skill would therefore have been motivated to have used Lucas' solubilizing compounds in the caspase assays of Landrum which also use rhodamine 110 as the assay compound, thereby assisting in the transfer of the assay compound into the intact cells, as disclosed by Lucas. A holding of obviousness over the cited claims is therefore required.

Claims 5-15, 20-22 and 38-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang et al (U.S. Pat. 6,248,904 B1).

As discussed above, Zhang discloses the use of derivates of the elected species of indicator moiety, rhodamine 110, in assays of whole cell enzyme activity, including caspase activity, for the purpose of ascertaining apoptotic as well as anticancer efficacy of therapeutic agents. As also discussed

above, Zhang discloses that additional solubilizing agents, such as DMSO, as well as liposomes or detergents, may be used to assist the transfer of the assay compounds into cells, and that Zhang is therefore considered to anticipate claims 5-9, 13-15, 38-40, 46, 48-51 and 54.

Zhang differs from claims 11, 12, 41 and 42 in failing to explicitly disclose a single embodiment combining the uptake-enhancing agent with multiple enzyme assays, either simultaneous or sequential, as recited in claims 11, 12, 41 and 42, or the use of 20 to 60% DMSO as the solubilizing agent, as recited in claims 20-22.

However, Zhang clearly discloses that different disease states can be assayed using different enzyme assays. See discussion at column 5 line 4 through column 6, line 15. The artisan of ordinary, recognizing that the enzyme assays for disease diagnosis would have been suitably performed either sequentially or simultaneously, clearly would have been motivated to have performed the assays using either tactic, reasonably expecting to generate the disease diagnosis regardless of whether the assays were performed at the same time, or one after the other. Thus, the claimed combination of uptake-enhancing agent with multiple enzyme assays clearly would have been obvious in view of Zhang's disclosure, the artisan of

ordinary skill recognizing the advantages of solubility agents as disclosed by Zhang's, and also recognizing the suitability of multiple enzyme assays to generate the data set disclosed by Zhang as being required for accurate disease diagnosis. A holding of obviousness over claims 11, 12, 41 and 42 is therefore required.

As to the amount of DMSO recited in claims 20-22, note specifically that Lucas clearly discloses that the artisan of ordinary skill would have recognized that using differing concentrations of solubilizing component would have resulted in different results. Thus, the artisan of ordinary skill would have considered the concentration of solubilizing component to be a result-effective parameter which would have been routinely optimized. The claimed concentration of DMSO must be considered obvious absent some demonstration that said concentration confers an unexpected result upon the claimed subject matter. A holding of obviousness is therefore required over claims 20-22.

Further still, assays of intensity or magnitude over time were well known in the art at the time of applicant's invention. Absent some demonstration that these assays perform in a manner unexpected in view of the prior art, a holding of obviousness over the cited claims is clearly required.

In sum, because the prior art fairly suggests the claimed subject matter, a holding of obviousness is clearly required.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Francisco C Prats whose telephone number is 703-308-3665. The examiner can normally be reached on Monday through Friday, with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G Wityshyn can be reached on 703-308-4743. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Francisco C Prats
Primary Examiner
Art Unit 1651

FCP
July 22, 2003